

## LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

# Cancer Drugs Fund rapid reconsideration of NICE Guidance TA295

## Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy

[ID1011]

Confidential until  
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**CONTAINS CIC/AIC**



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# **1 INTRODUCTION**

The National Institute for Health and Care Excellence (NICE) is in the process of assuming responsibility for the Cancer Drugs Fund (CDF). The CDF provided a mechanism for some cancer treatments which failed to receive a positive recommendation when originally appraised for clinical and cost effectiveness for general use in the NHS, to be provided on a case-by-case basis to selected patients referred to the CDF by their clinician. As part of the transition, a number of historic technology appraisal decisions are being rapidly reconsidered to determine the future status of treatments currently provided only through the CDF, i.e. whether they may now be recommended for general use, continue within the scope of the revised CDF scheme, or not be provided at all through the NHS. The Liverpool Reviews and Implementation Group (LRiG) at the University of Liverpool has been commissioned to review the company submission (CS) to assist a NICE Appraisal Committee (AC) in reconsideration of NICE Guidance TA295. The original Single Technology Appraisal (STA) was conducted in 2012-13 and final NICE guidance was issued in August, 2013 and did not recommend everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy for use in the NHS.

## **2 CONTEXT AND APPROACH TO RAPID RECONSIDERATION**

To allow these rapid reconsideration exercises to proceed with the minimum risk of delay, the expected procedures have been restricted in scope for the company making a resubmission and for the Evidence Review Group (ERG) who is tasked with providing an independent assessment of the CS. It is assumed that the primary clinical effectiveness data will remain essentially unchanged from the original appraisal and therefore no additional clinical evidence will be accepted by NICE. The cost effectiveness analyses included in the CS needs to reflect the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) (ICERs) as identified in the published guidance. It is anticipated that the main areas to be considered by the AC will relate to changes in the costs associated with treatment including any special NHS pricing agreements that have been agreed since the original STA was carried out.

## **3 SPECIFIC DIFFICULTIES WITH THIS RAPID RECONSIDERATION**

An outline of process is provided to companies that are planning to make a submission to NICE for reconsideration of a treatment previously not recommended for general NHS use.

In contrast to this outline of process, the company indicated that they wished to submit updated survival data from the key clinical trial (BOLERO-2), as these data were now available. The ERG advised NICE that these updated survival data could only be accommodated within the defined process, if the ERG were permitted access to additional detailed evidence related to the latest trial survival results in the form of a request for clarification. NICE therefore approached the company and asked them to provide specific information as put in writing by the ERG.

## 4 MODEL ALTERATIONS

The company has submitted a revised version of the decision model developed for the original appraisal. In addition to implementing amendments identified previously by the ERG, the company has employed a different approach to estimating time-to-event patterns (especially overall survival [OS]) and this has led to structural changes to parts of their model.

### 4.1 *Implementing ERG recommended amendments*

The NICE guidance issued in 2013 included a detailed list of preferences as expressed by the AC that identified features of the cost effectiveness model and model parameters that formed the basis for their decision. The ERG has examined the revised version of the company model and sought to verify whether the company has implemented the required alterations. Within the time available, the ERG can confirm, as far as it is able, that all required changes have been applied by substitution of revised parameter values or by coding modifications.

One issue of concern with the version of the company model submitted for this Rapid Reconsideration is that the time horizon for the model calculation has been reset to 15 years, contrary to the setting in the original model (10 years). This has the effect of artificially reducing the size of estimated ICER by between £3,000 and £6,000 per quality adjusted life year (QALY) gained.

However, closer examination of the model coding has revealed an error in the implementation of the time horizon so that the model results are generated for the wrong time period to that specified by the user. The ERG has corrected this error and then explored the sensitivity of the model results to different time horizons. The ERG considers that the estimated ICER per QALY gained is generally stable across a wide range of time horizons, but that the incremental OS is more accurately represented when results are calculated for

extended periods. For the purposes of generating cost effectiveness results in this Rapid Reconsideration, the ERG has adopted a time horizon of 20 years.

## **4.2 Survival extrapolation**


In view of the inclusion of new survival data relating to extended follow-up to the key BOLERO-2 clinical trial in the new submission, the ERG forwarded a clarification request via NICE for detailed Kaplan-Meier (K-M) analysis results for three variables: OS, progression-free survival (PFS) and post-progression survival (PPS), using an alternative censoring rule to avoid a type of right-censoring bias can occur in trials with a substantial proportion of patients who are censored at data cut-off. This is similar to the clarification requests made during the original STA, which the company did not carry out.

The company noted that the alternative censoring method is not the standard approach to analysing K-M data, and identified difficulties in applying it because of the way BOLERO-2 data were captured and recorded (especially for patients withdrawing consent). However, the company adapted the ERG requests to the BOLERO-2 data as best as possible, and provided recensored results for PFS and OS. However, the company did not provide the requested PPS analysis as they considered this to lack statistical validity.

The ERG understands that there is a balance to be struck between possibly unrecorded events prior to data cut-off, and excessive under-attribution of exposure time prior to data cut-off. However, in a well conducted clinical trial, patient status ascertainment, especially at a planned analysis milestone, should be a priority and therefore subject to a relatively low risk of event omission (especially for deaths). In reported results from a number of clinical trials submitted as evidence in previous NICE appraisals, the ERG has observed patterns of survival consistent with excessive 'undercounting' of exposure time prior to data cut-off leading to distortion of survival curves and the consequent miscalibration of parametric survival functions. Only by comparing results using alternative censoring definitions is it possible to assess whether significant differences in outcomes may be related to the method of censoring, and, if so, to quantify the likely impact of such differences on estimated cost effectiveness.

### **4.2.1 Progression-free survival**

The two sets of trial data were compared to assess the influence of censoring method on PFS outcomes.

In the everolimus treatment arm, the PFS survival estimates are identical up to 302 days from randomisation, but then begin to separate to a maximum difference of .

██████████) in the 2016 analysis compared to the earlier analysis. This then reduces steadily to ██████████ at the end of the observed data set. A similar pattern of PFS estimates in the exemestane only arm is observed, although the maximum difference is ██████████, reducing to ██████████. Thus the influence of using an alternative censoring is small, but tends to favour treatment with everolimus+exemestane.

In this report, the ERG has chosen to base its estimates on the recensored trial results.

Analysis of the BOLERO-2 trial K-M data for PFS confirms that a simple exponential model (i.e. constant risk of disease progression or death) fits both arms of the trial closely. The ERG has therefore used the K-M data directly to populate the decision model, until a point beyond the strong cyclic behaviour associated with scheduled assessments at which the trial data and exponential model are closely aligned, after which the modelled extrapolation was applied. This occurred after 12 months in the intervention arm and after 11 months in the control arm as illustrated in Figure 1.

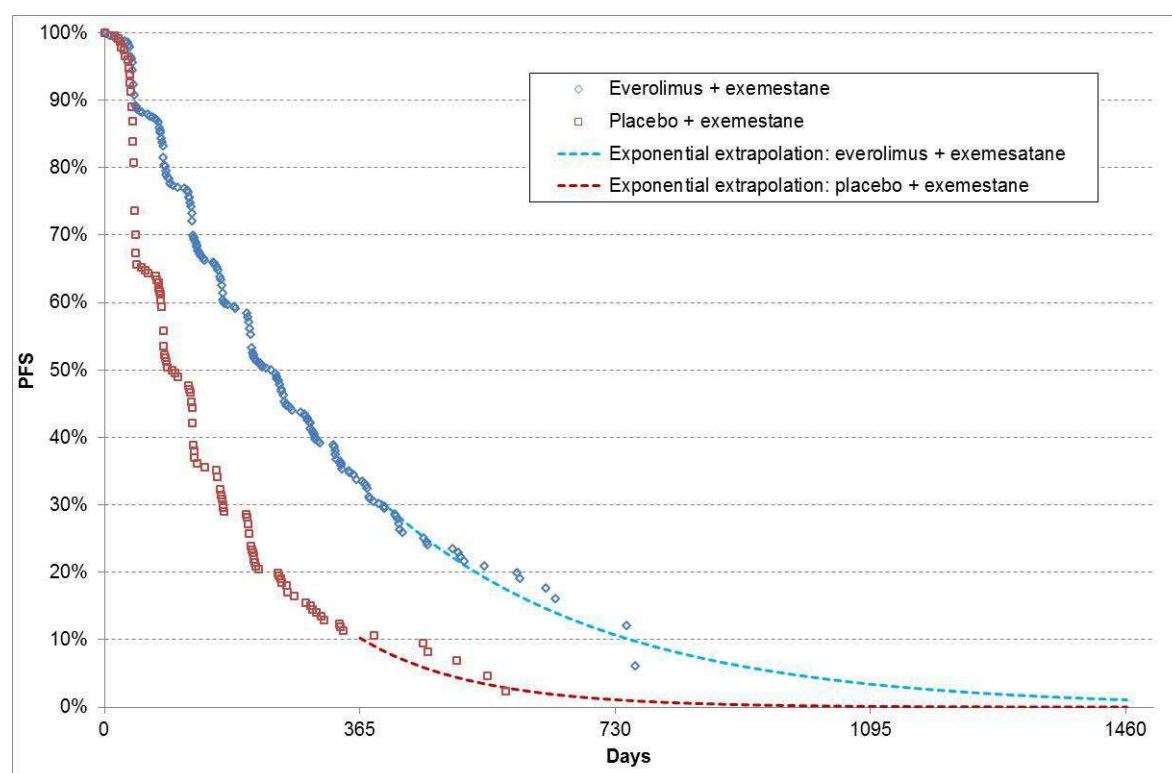


Figure 1 Progression-free survival K-M estimates (BOLERO-2 clinical trial) with exponential extrapolation curves applied in the decision model after 11 or 12 months

#### 4.2.2 Overall survival

In the absence of direct evidence on the relative prognosis for BOLERO-2 trial patients beyond disease progression (PPS), the ERG has tested a conservative assumption of efficacy i.e., that the survival benefit from everolimus+exemestane versus

placebo+exemestane is limited to the pre-progression phase, so that thereafter mortality rates are the same in the two trial arms. This hypothesis would imply that mortality would be delayed in the intervention arm by use of everolimus, so that the survival curve would be moved forward in time (i.e. to the right in the OS chart), so that the gap between the two curves reflects the mean survival gain attributable to everolimus. However, this hypothesis also implies that over time as the proportion of surviving patients still progression-free reduces towards zero, the pattern of mortality should become similar in the two trial arms.

The ERG carried out an exploratory analysis by progressively shifting the survival plot of the BOLERO-2 placebo arm until the best fit was obtained to the later stage of the everolimus arm by visual inspection. This is illustrated in Figure 2, and suggests that there is a close correspondence of long-term survival trends beyond the point at which estimated OS is 62% (point C).

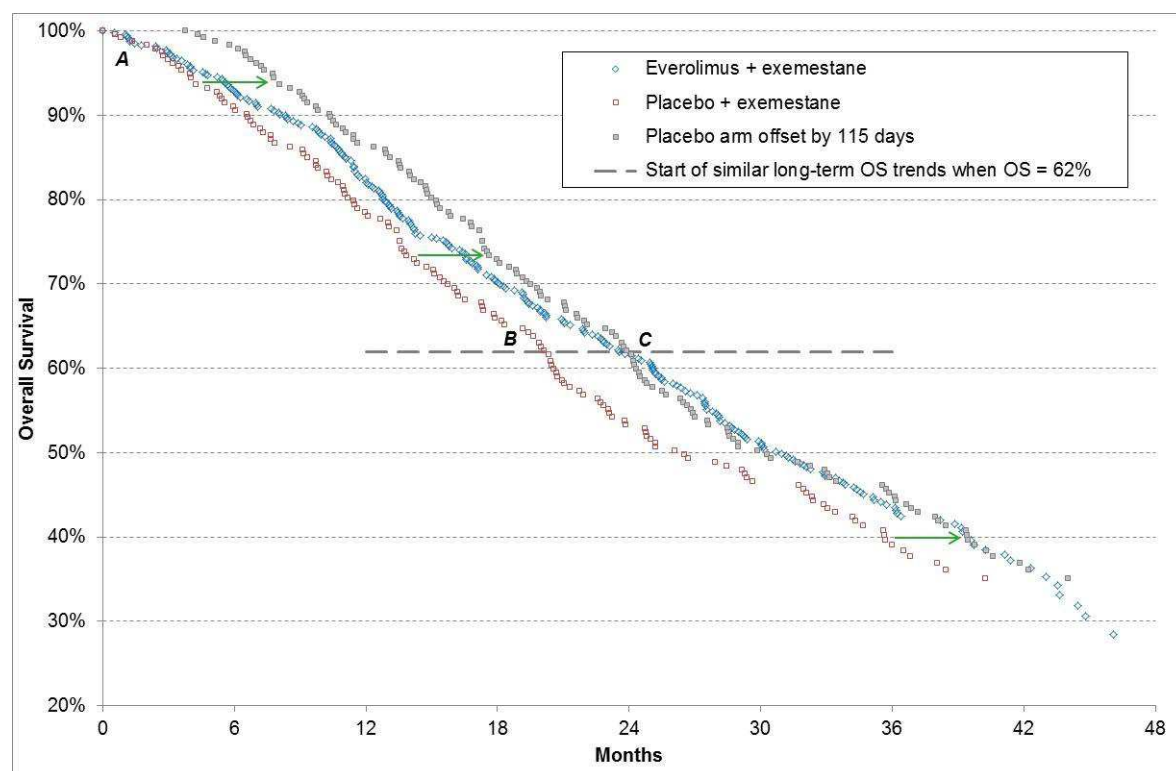


Figure 2 Overall survival in BOLERO-2 clinical trial, with offset placebo arm to compare long-term survival patterns

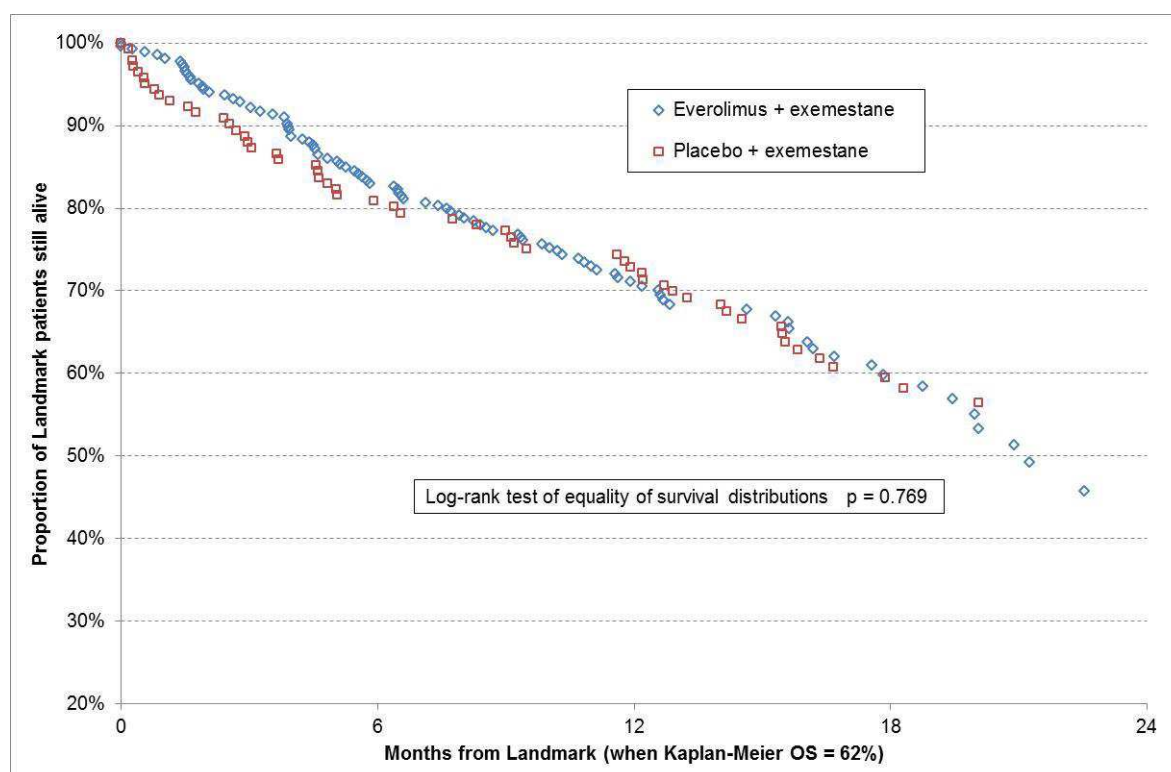


Figure 3 Landmark analysis of long-term survival for patients still alive when estimated OS is 62% in the BOLERO-2 clinical trial

This was confirmed by a K-M landmark analysis of all patients still at risk at the times corresponding to the 62% OS landmark (Everolimus+exemestane [REDACTED] patients and [REDACTED] events, Placebo+exemestane [REDACTED] patients and [REDACTED] events) (Figure 3). The estimated mean conditional OS was estimated at [REDACTED] days ([REDACTED]) for Everolimus+exemestane versus [REDACTED] days ([REDACTED]) for Placebo+exemestane.

However, the Log Rank (Mantel-Cox) test of equivalence indicated that there was no statistical basis for considering that patients in the Placebo+exemestane arm experienced a greater long-term survival ( $\chi^2 = 0.0861$ , 1 degree of freedom,  $p=0.7692$ ). Therefore it was assumed that a common survival trend applied to all patients beyond the landmark point. This is consistent with an assumption that all patients who suffer a non-fatal progression event have the same prognosis irrespective of prior treatment, with an estimated mean conditional survival of [REDACTED] days ([REDACTED]).

A direct consequence of this finding is that the difference in OS attributable to everolimus can be accurately estimated directly from the trial results, without any recourse to parametric survival modelling. This is because the long-term survival of the 62% of everolimus+exemestane patients alive at point B in Figure 2 is can be considered identical to



the long-term survival of the 62% of placebo+exemestane patients at point C in Figure 2 so that long-term survival makes no contribution to the net difference in OS, regardless of the form of the common long-term survival trend. As a consequence, the true OS gain is simply calculated as the difference between the area under the intervention survival curve from point A to point C and the area under the control survival curve from point A to point B. This amounts to [REDACTED] months (95% CI [REDACTED] months).

The choice of 62% as the starting point for the long-term phase of survival is convenient because a common starting point for extrapolation excludes any risk of starting-point bias. Many other choices might be considered, but would require more time than was available to the ERG.

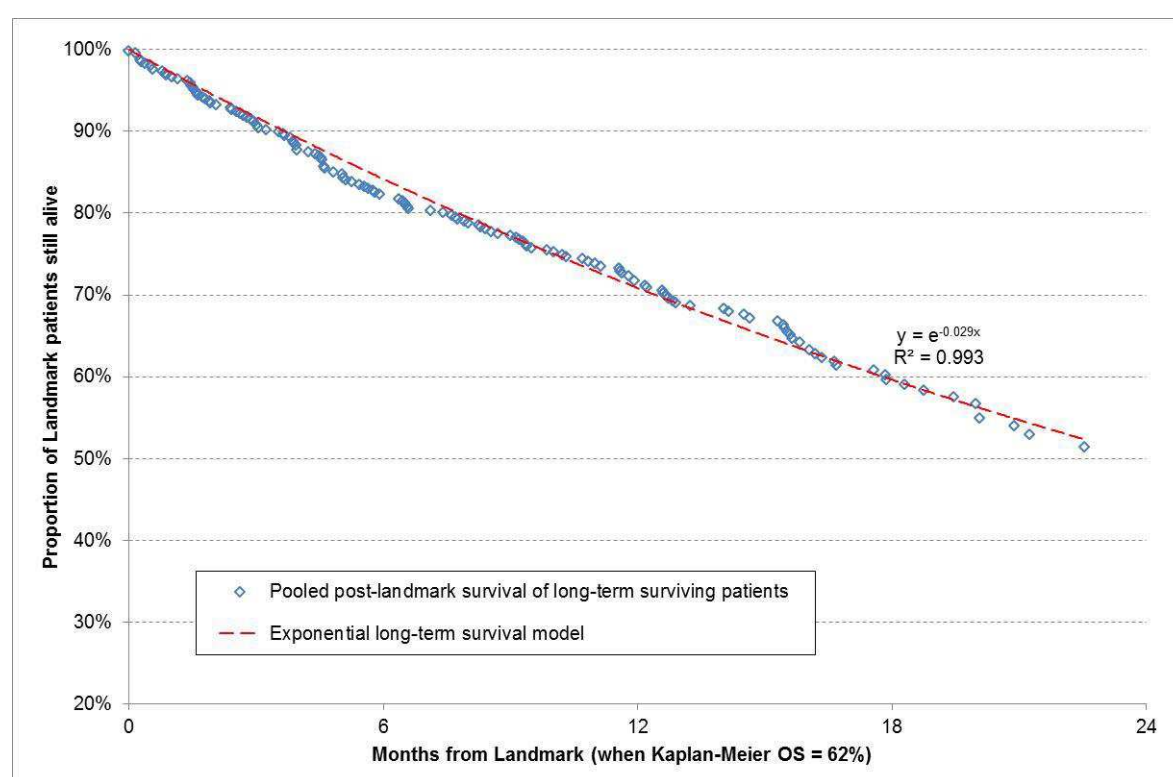


Figure 4 Exponential parametric model fitted to pooled long-term OS data (beyond the landmark) from BOLERO-2 clinical trial

For the purpose of reproducing these findings in the decision model it is necessary to identify a representative projective function for long-term survival (equivalent to post-progression survival). Figure 4 shows the results of a K-M landmark analysis of the BOLERO-2 long-term trial data pooled across the two trial arms (assuming equivalence). It is clear that a simple exponential provides an excellent fit, indicating a constant annual mortality rate of [REDACTED],



equivalent to an expected mean long-term survival (for patients surviving at the landmark) of ■■■ years.

### **4.3 'End of Life' criteria**

The company refers to evidence from clinical trials to support a case for the application of NICE 'End of Life' criteria:

- In the BOLERO-2 clinical trial, the reported difference in median OS of 4.4 months (31.0 versus 26.6 months) indicates that a survival benefit greater than 3 months is confirmed.
- In the SoFEA clinical trial, the median OS in both arms of the trial was less than 24 months.

The use of the median as a measure of survival benefit is problematic on several grounds. First, the median is not the natural metric for cost effectiveness analysis; cost effectiveness analysis relies on mean outcomes and mean costs. Second, the median is calibrated on only a subset of the trial data (i.e. the first 50% to suffer the measured event) and ignores the remaining trial data. Third, the median is a completely arbitrary reference point as any other percentile could be used and may give very different results.

Figure 5 shows how the estimated OS gain varies in the BOLERO-2 clinical trial depending on which measure is selected to represent the whole data set. Clearly the median (50%) suggests the greatest benefit, but other options all appear to show less advantageous results. The ERG estimated mean lies centrally within the range of percentile measures, since it takes account of the whole available data set and is therefore representative of the overall experience of the patient population. For example, if the 45th percentile is used (based on 3-4 months additional data), the estimated OS gain falls to only ■■■ months.

Figure 5 Comparison of estimated OS gain attributable to everolimus for a range of survival percentile points.

The ERG notes that the company used the SoFEA trial to demonstrate that life expectancy in this patient group is less than 24 months. The company has based this justification on two grounds:

1. The SoFEA trial provides a robust analysis of survival specific to the UK
2. The SoFEA was used in the original submission and the company has had the SoFEA data set re-analysed to remove the HER2+ve patient population.

However, based on the analyses described above, the ERG estimates the mean OS in the control arm of the BOLERO-2 trial to be [REDACTED] months (compared to [REDACTED] months for the everolimus arm). The ERG therefore considers that there is substantial uncertainty since, on the basis of the available evidence, everolimus+exemestane does not fulfil the criteria for consideration as an 'End of Life' treatment. This conclusion accords with the assessment made during the original STA.

## 5 RESULTS

Table 1 summarises the cost effectiveness results obtained using the revised decision model submitted by the company, alongside results using the ERG corrected and revised model including the ERG remodelled OS and PFS estimates. In all scenarios the reduced price of everolimus improves the size of the estimated ICER per QALY gained, as does the correction made by the ERG to the time horizon model logic. The reworking of the PFS evidence by the ERG substantially increases the size of the ICER per QALY gained (as it both increases net costs and reduces QALYs in the everolimus+exemestane arm), whereas the OS remodelling has only a minor effect (reducing both costs and QALYs in parallel).

Table 1 Revised cost and outcome effects of ERG model amendments relative to the company's base case analysis, with and without PAS price

Model Scenario	Company revised model (no PAS)	Company revised model (with PAS)	ERG corrected model (no PAS)	ERG corrected model (with PAS)	ERG model + PFS revision (with PAS)	ERG model + OS revision (with PAS)	ERG model + both revisions (with PAS)
Everolimus Cost	£49,748	██████	£63,498	██████	██████	██████	██████
Everolimus QALYs	1.581	██████	2.082	██████	██████	██████	██████
Everolimus Life years	2.796	██████	4.090	██████	██████	██████	██████
Exemestane Cost	£36,677	██████	£51,177	██████	██████	██████	██████
Exemestane QALYs	1.367	██████	1.825	██████	██████	██████	██████
Exemestane Life years	2.636	██████	3.899	██████	██████	██████	██████
<b>Incremental Cost</b>	<b>+£13,070</b>	██████	<b>+£12,321</b>	██████	██████	██████	██████
<b>Incremental QALYs</b>	<b>+0.214</b>	██████	<b>+0.256</b>	██████	██████	██████	██████
<b>Incremental Life years</b>	<b>+0.160</b>	██████	<b>+0.191</b>	██████	██████	██████	██████
<b>Estimated ICER</b>	<b>£61,046</b>	██████	<b>£48,073</b>	██████	██████	██████	██████
ICER change	-	██████	-£12,973	██████	██████	██████	██████

ERG model estimates are for 20 year time horizon. Life years are undiscounted

## 6 CONCLUSION

The revised decision model submitted by the company includes a new module to include additional parametric modelling undertaken since the original STA. In order for the ERG to take account of the survival outcome data for extended follow-up of the BOLERO-2 clinical trial, it was necessary for the ERG to undertake additional analyses. The results of the analyses revealed that conventional survival modelling using standard parametric functions was neither accurate nor in fact necessary in order to obtain robust estimates of mean expected patient survival times. ERG re-estimation of PFS was found to both increase incremental costs and reduce incremental QALYs, thus increasing the size of the ICER per QALY for everolimus+exemestane versus exemestane, whereas the amended OS data led to only minor changes in model costs and outcomes.

In the course of implementing the results of the ERG investigations within the company model, a logic error was identified relating to misspecification of the model time horizon which prevented long-term survival from being accurately estimated within the model. This has been corrected and all of the model results from the ERG corrected version are based on a 20 year time horizon in order to capture all future effects.

## 7 REFERENCES

1. National Institute for Health and Care Excellence (NICE). NICE Technology Appraisal Guidance[TA295]. 2013 [August]; Available from: <https://www.nice.org.uk/guidance/ta295>
2. Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, et al. Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer. *N Engl J Med* 2012;366(6):520-9
3. Johnston SRD, Kilburn LS, Ellis P, et al. 2015 Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial *Lancet Oncology* 14;10:989-998

## APPENDIX: MODEL AMENDMENTS

### Details of amendments made by the ERG to the company's revised decision model

#### Time horizon referencing logic

This revision corrects a referencing error which sets the time horizon 12 months shorter than is selected by the user.

Select range Results!D113:E120. Copy and paste to range D112:E119

Set value in Cell Results!B120 to 10

Set value in Cell Results!C120 to '30 years

Set value in Cell Results!D120 to 360

Set value in Cell Results!B120 to 10

#### ERG OS and PFS estimates

A new table of ERG PFS and OS estimates has been copied into worksheet 'Survival' with top-left of the new table located at cell AM7.

The table is provided in a separate confidential Excel file.

Two binary switch variables should be created on the 'Results' worksheet, with names 'ERG\_1' and 'ERG\_2'.

ERG\_1 is set by the user to either 0 or 1 and determines which values are used to estimate PFS (0 gives the original company survival, 1 gives the ERG survival estimates)

ERG\_2 is set by the user to either 0 or 1 and determines which values are used to estimate OS (0 gives the original company survival, 1 gives the ERG survival estimates)

#### On Worksheet 'Effectiveness':

Edit the formula in **Cell W35** as follows:

=IF(ERG\_1=0,MIN(CHOOSE(index\_pfs\_function\_EVE,Survival!D9,Survival!E9,Survival!F9,Survival!G9,Survival!H9),X35),Survival!AN9)

Edit the formula in **Cell X35** as follows:

=IF(ERG\_2=0,CHOOSE(index\_os\_function\_EVE,Survival!I9,Survival!J9,Survival!K9,Survival!L9,Survival!M9),Survival!AO9)

Edit the formula in **Cell Y35** as follows:

=IF(ERG\_1=0,MIN(CHOOSE(index\_pfs\_function\_COMP,Survival!P9,Survival!Q9,Survival!R9,Survival!S9,Survival!T9),Z35),Survival!AP9)

Edit the formula in **Cell Z35** as follows:

=IF(ERG\_2=0,CHOOSE(index\_os\_function\_COMP,Survival!U9,Survival!V9,Survival!W9,Survival!X9,Survival!Y9),Survival!AQ9)

Select & Copy Range Effectiveness!**W35:Z35**

Paste formulae to Range Effectiveness!**W36:Z635**